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Long-term moxifloxacin in complicated tuberculosis patients with adverse reactions or resistance to first line drugs

Luigi Ruffo Codecasa[a,*,1], Giovanni Ferrara[b,1], Maurizio Ferrarese[a], Maria Antonietta Morandi[a], Valeria Penati[c], Carla Lacchini[c], Patrizia Vaccarino[c], Giovanni Battista Migliori[d]

[a]*TB Unit, Villa Marelli Inst., Niguarda Hospital, Regional Reference Centre for TB, Viale Zara 81, 20159 Milan, Italy*
[b]*Section of Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy*
[c]*Mycobacteriology Laboratory, Regional TB Reference Center, Villa Marelli Institute, Niguarda Ca' Granda Hospital, Milan, Italy*
[d]*WHO Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Tradate, Italy*

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Summary
Study objectives: To test safety and tolerability of long-term moxifloxacin in resistant tuberculosis (TB) patients and patients with intolerance to first line anti-TB drugs.
Design: Clinical evaluation of adverse events (AEs) during prolonged moxifloxacin treatment.
Setting: TB Unit of the Regional TB Reference Center, Villa Marelli Institute, Niguarda Ca'Granda Hospital, Milan, Italy
Patients and interventions: Patients treated with moxifloxacin, 400 mg orally once daily for TB in the Villa Marelli Institute from January 2001 to December 2003 were enrolled.
Results: Thirty-eight patients were treated with moxifloxacin at the Villa Marelli Institute in the study period, for multidrug resistant (MDR) TB (14, 36.8%), for intolerance to first line anti-TB drugs (9, 23.7%), for combined resistance and intolerance to first line anti-TB drugs (12, 31.6%), other reasons (3, 7.9%). The mean duration of moxifloxacin treatment was 6.3±5.2 months. Twelve (31.6%) patients

Abbreviations: TB, Tuberculosis; Multidrug-resistant; WHO, World Health Organization; MTB, Mycobacterium Tuberculosis Complex; AE, Adverse event

*Corresponding author. Tel.: +390264445833; fax: +390264445826.
E-mail address: luigiruffo.codecasa@fastwebnet.it (L.R. Codecasa).

[1]Both authors equally contributed to this manuscript.

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reported at least an AE due to moxifloxacin, mostly gastrointestinal (8, 21.0%), general (5, 13.2%) and central nervous system (3, 7.9%) AEs. In 4 (10.5%) patients the drug was withdrawn for major AEs; no irreversible or fatal events were recorded. Most of the patients (31, 81.6%) reported a treatment success, even if the success rate was lower in MDR TB patients (8/14, 51.7%).
Conclusions: Despite the fact that a large proportion of patients experienced at least an AE due to moxifloxacin, the drug resulted safe in the long-term administration for complicated TB cases.

Introduction

The increasing prevalence of resistance to first line anti-tuberculosis (TB) drugs in countries with a high incidence of TB is a challenge to control programmes based on the World Health Organisation-recommended strategy (DOTS strategy).[1] High rates of failure and relapses are recorded when standard (or poorly modified) regimens are used for resistant and multidrug-resistant (MDR) TB cases.[2,3] The development and implementation of the DOTS plus strategy is crucial in the fight against TB at a global level, and new regimens, including second line and new anti-TB drugs, are urgently needed.[4]

New drugs highly active against *Mycobacterium tuberculosis* (MTB) could improve treatment of cases with resistance to first line drugs (especially to isoniazid and rifampicin) and may shorten the duration of current standard regimens. An ideal drug should be highly active against MTB, it should allow a once a day administration and it should be well tolerated and safe, even in long-term regimens. Quinolones are the first new class of drugs introduced on the market with a proven in vitro activity against MTB since rifampicin and interest is increasing about their potential use both in the treatment of complicated cases of TB and of latent TB infection.[4] Despite limited evidence is available, the current lack of choices makes the newer quinolones the first alternative to rifampicin[5] and an asset for regimens tailored to treat MDR TB.[6] New generation quinolones had been repeatedly reported to have lower minimal bactericidal concentrations (MBCs), to be better tolerated, especially in prolonged administration[7,8] and to improve treatment outcomes[9] of MDR TB cases. Sparfloxacin was reported to be safe and effective in a prospective series of patients with complicated TB,[10] even though its use is limited by AEs such as photosensitazion.[11] Retrospective series of patients showed that levofloxacin is well tolerated,[12] and may be more effective than ofloxacin.[13]

Moxifloxacin has the highest in vitro activity against MTB[14] and its effect in vivo was demonstrated in a recent study aimed to assess the effect on bacterial growth in patients with active pulmonary TB.[15]

Very limited data are available on the safety and tolerability of moxifloxacin in patients treated either for drug resistant TB or because of intolerance to first line drugs.[16]

We report the results of an observational study on the use of moxifloxacin 400 mg orally once daily, given in combination with other anti-TB drugs for the treatment of complicated TB patients, in order to assess its safety and tolerability in long-term treatment. Treatment outcomes are also reported.

Materials and methods

Setting

The Villa Marelli Institute is an out-patient care TB Unit with a catchment area of about 4 million people. Patients diagnosed in the Institute or in other hospitals of Lombardia Region are referred to the TB Unit for treatment and follow up. The Unit is a national reference centre for the treatment of MDR TB cases. Its microbiology laboratory is the National Reference Laboratory for Drug Susceptibility Testing (DST) for mycobacteria, being part of a national network of laboratories fulfilling the principles of the Global Project on Anti-TB Drug Resistance Surveillance (GPDRS). The DSTs for all the patients described in this study were performed for first line anti-TB drugs (except pirazinamide) and ofloxacin, according to the proportion method. The quality of DSTs is ensured by a once-a-year supranational proficiency testing, performed according to international standards.[17]

Study design and protocol

All the 1231 TB patients, undergoing a complete set of clinical, microbiological and laboratory examinations at diagnosis and during follow-up (e.g. medical assessment, chest radiographies and blood

tests-including liver and renal function, blood cell count and some other methabolic parameters such as uric acid and glycemia-monthly or every 2 months according to the phase of treatment, the case severity and evolution) treated at the study site between January 1, 2001 and December 31, 2003 were enrolled. All their data were prospectively recorded in an electronic database.

In particular, at each control visit all patients were interviewed twice by a public health nurse and subsequently by a chest physician about their adherence to treatment and onset of AEs, all data being recorded on their file.

Patients receiving 400 mg orally once daily of moxifloxacin (Avalox©, Bayer Pharmaceuticals, Milan, Italy) were retrospectively considered for analysis of AEs due to this antibiotic. Reasons for prescribing moxifloxacin were classified as resistance to first line drugs, intolerance to first line drugs or other reasons. The study was approved by the local ethics committee.

Anti-TB regimens included at least 3 active drugs, selected on the basis of DST results.[18] For MDR TB patients a treatment of at least 18 months was programmed according to internal protocols.

Definitions recommended by WHO guidelines[18] are implemented in the Unit and anti-TB regimens are prescribed following major international guidelines.[5,18] An immigrant was defined as a person born in a country outside the European Union and the other industrialized countries.[19]

MDR TB was defined as TB caused by strains of MTB with a proven resistance to at least rifampicin and isoniazid.[20]

Intolerance (as an inclusion criteria) was defined as the occurrence of major AEs not allowing the administration of a determinate drug to the patient.

AEs were classified as minor (not implying the withdrawal of the drug) and major (causing the discontinuation of the drug) according to WHO guidelines.[18] Criteria for attributing the AE to moxifloxacin were their onset with the administration of the drug, the resolution (or improvement in case of not reversible or partially reversible AEs) with the withdrawal of the drug, the type of AE (including only AEs most likely due to moxifloxacin or quinolones, as reported in the literature[8]). In detail, when AEs occurred, the drugs most likely related to the phenomenon were temporarily discontinued and then separately reintroduced in order to assess their relation to symptoms.

Data analysis

Sensitive variables from patients treated with moxifloxacin were analysed, including demographic data (gender, age, ethnicity, immigration status), TB case definition and category, pattern of resistance as reported in the DST at the time of the first administration of the drug, presence of intolerance/major AEs to first line drugs, initial and modified regimens adopted, duration of the use of moxifloxacin, results of blood tests performed before and during the treatment, concomitant anti-TB drugs. Outcomes of patients were recorded, and stratified for MDR TB patients and patients treated with moxifloxacin because of intolerance to first line drugs.

Expected and observed frequencies were compared by χ^2 test. A p value $\leqslant 0.05$ was considered statistically significant.

Results

Thirty-eight patients (3.1% of all the cohort) were prescribed anti-TB regimen containing moxifloxacin for the treatment of active TB. The main reasons to prescribe the drug were multidrug-resistance to first line drugs alone (14 out of 38 patients, 36.8%), intolerance to standard anti-TB treatment (9 patients, 23.7%), combined resistance (excluding MDR) and intolerance to first line drugs (12 patients, 31.6%), other reasons (3 patients, 7.9%). In details, in these latter 3 patients anti-TB regimen included moxifloxacin respectively because of a previous anti-TB therapy completion and relapse in a HIV seropositive patient; a relapse in a patient with a psoas muscle abscess; progression of disease during therapy (1 patient).

Main demographic features of the patients, main features of the disease and risk factors for TB are reported in Table 1. Among the 26 patients with a resistant strains, 7 (18.4%) were resistant to isoniazid, 1 (2.6%) to rifampicin, 2 (5.3%) to isoniazid and pirazinamide, 1 (2.6%) to isoniazid and streptomycin and 14 (63.1%) were MDR TB strains.

The mean duration of any anti-TB treatment in the study group was 9.2 ± 5.6 months. In the MDR subgroup treatment lasted 17.3+6.8 months.

The mean duration of moxifloxacin treatment was 6.3 ± 5.2 months (median 5.7 months, ranging from few days to 20.8 months). Table 2 shows the anti-TB drugs used in combination with moxifloxacin. Thirty-two (84.2%) patients reported one or more AEs during the administration of the combined anti-TB treatment (Table 3). Overall, most of the patients well tolerated moxifloxacin for the duration of the treatment (26 out of 38, 68.4%). Twelve (31.6%) patients reported at least an AE

Table 1 Demographic features, WHO categories, main risk factors for TB in the patients before being treated with Moxifloxacin at the Villa Marelli Institute, Milan, Italy 2001–2003.

Features	*N* (%)
Main demographic features	
Age (mean ± SD)	43.6 ± 17.3
M/F	17/21 (44.7)
Immigrants	22 (57.9)
Weight (mean ± SD)	58.5 ± 10.9
TB localization	
Pulmonary TB	25 (65.8)
Extra-pulmonary TB	6 (15.8)
Pulm. and extra-pulm. TB	7 (18.4)
TB category	
First diagnosis	18 (47.4)
Relapse	14 (36.8)
Chronic	4 (10.5)
Other	2 (5.3)
Risk factors for TB	
Diabetes	2 (5.3)
Contact	14 (36.8)
Intravenous drugs	2 (5.3)
Alcohol	4 (10.5)
Viral hepatitis	2 (5.3)
Cancer	1 (2.6)
HIV seropositive status	2 (5.3)
Reason for prescribing moxifloxacin	
Resistance to first line drugs	14 (36.8)
Intolerance	9 (23.7)
Combined resistance and intolerance	11 (29.0)
Other reasons	4 (10.5)
Total	38 (100.0)

related to the use of moxifloxacin, which occurred randomly throughout the treatment course. Seven patients (18.4%) needed a temporary discontinuation of the drug, mainly for nausea and vomiting, asthenia and anorexia. One of them reported tremors. A woman reported genital pain during the treatment with moxifloxacin, which disappeared with the discontinuation and not represented when the drug was re-introduced. All these patients did not present further AEs with moxifloxacin re-challenge.

Four (10.5%) out of the 12 (4/12, 33.3%) patients reporting AEs due to moxifloxacin needed the discontinuation of the treatment for one or more major AEs. Main AEs reported by these patients were nausea (2 patients) and vomiting (1 patient), muscle pain (1 patient), dizziness and insomnia (1 patient), tremors (1 patient). One patient presented vaginitis.

Table 2 Anti-TB drugs used in combination with moxifloxacin in the TB patients treated at the Villa Marelli Institute, Milan, Italy 2001–2003.

Drug	*N* (%)
Moxifloxacin	38 (100)
Amikacin	6 (15.8)
Para-aminosalicylic acid	4 (10.5)
Clarithromycin	2 (5.3)
Ethambutol	28 (73.6)
Ethionamide	14 (36.8)
Isoniazid	10 (26.3)
Prothionamide	3 (7.9)
Pyrazinamide	20 (52.6)
Rifabutin	3 (7.9)
Rifampicin	17 (44.7)
Streptomycin	1 (2.6)
Terizidone	10 (26.3)

Treatment success (the sum of WHO categories cured and treatment completed) was obtained in 31 (81.6%) patients. In particular, the success rate was significantly lower in MDR TB patients (8/14, 51.7%) than in patients treated with moxifloxacin for other reasons (23/24, 95.8%, $P = 0.01$). Three (7.9%) patients were defined as chronics at the end of the treatment, 2 (5.3%) were lost and 2 (5.3%) MDR TB patients died (for reasons independent by the moxifloxacin administration).

Discussion

Retrospective data have shown that the use of quinolones is associated to a better outcome in MDR TB cases[9] and that newer molecules of this class may be better tolerated and more effective.[13] Few data are available on the safety and tolerability of newer quinolones in long-term anti-TB regimens.[10,12] Moxifloxacin is a very promising drug, because of the lowest minimal bactericidal concentration (MBC) in vitro against MTB,[14] and recent in vivo data.[21] However, the combination with other anti-TB drugs and high dose of moxifloxacin may be needed to prevent the development of resistance.[22] To the date, no fatal reaction due to moxifloxacin administration has been reported, but very limited data are available on long-term use, especially in combination with other anti-TB drugs.

To our knowledge only case reports are available on moxifloxacin safety in complicated TB cases. Many of them were MDR TB patients, and the use of the drug was considered life-saving. Other patients were given moxifloxacin because of poor

Table 3 Main adverse events (AE) reported by patients treated with moxifloxacin at the Villa Marelli Institute, Milan, Italy 2001–2003, classified for AEs due to the overall anti-TB treatment (mean duration of the therapy 9.2±5.6 months (median 8.3 months, range 1.6–23.4 months) and to moxifloxacin and 6.3±5.2 months (median 5.7 months, ranging from few days to 20.8 months), respectively).

	Anti-TB treatment	Moxifloxacin
	N (%)	
Total	(38)100	
Patients reporting AEs	32 (84.2)	12 (31.6)
Gastrointestinal disorders	20 (52.6)	8 (21.0)
Abdominal pain	5 (13.2)	1 (2.6)
Constipation	1 (2.6)	—
Diarrhoea	5 (13.2)	—
Dyspepsia	1 (2.6)	1 (2.6)
Haematemesis	1 (2.6)	—
Nausea	7 (18.4)	3 (7.9)
Vomiting	4 (10.5)	3 (7.9)
Nervous system disorders	16 (42.1)	3 (7.9)
Dizziness	1 (2.6)	1 (2.6)
Epilepsy	2 (5.3)	—
Paresthesia	2 (5.3)	—
Headache	5 (13.2)	—
Loss of consciousness	1 (2.6)	—
Tremors	4 (10.5)	1 (2.6)
Depression	1 (2.6)	—
Insomnia	2 (5.3)	1 (2.6)
General disorders	13 (34.2)	5 (13.2)
Asthenia	5 (13.2)	3 (7.9)
Oedema (site of administration)	1 (2.6)	—
Pain	1 (2.6)	1 (2.6)
Fever	3 (7.9)	—
Anorexia	3 (7.9)	1 (2.6)
Musculoskeletal system	6 (15.8)	2 (5.3)
Arthralgia	5 (13.2)	2 (5.3)
Myalgia	1 (2.6)	—
Eyes	4 (10.5)	1 (2.6)
Eye irritation	1 (2.6)	1 (2.6)
Visual disturbance	3 (7.9)	—
Infection-infestations	3 (7.9)	1 (2.6)
Abscess (site of administration)	1 (2.6)	—
Esophageal candidiasis	1 (2.6)	—
Vaginitis	1 (2.6)	1 (2.6)
Skin	3 (7.9)	—
Erythema	1 (2.6)	—
Rash macular	2 (5.3)	—
Ear and labyrinth disorders	1 (2.6)	—
Auditory deficit	1 (2.6)	—

tolerability to first line drugs or for other particular clinical conditions. Moxifloxacin was always used in combination with other first and/or second line drugs, and most of the patients reported side-effects to anti-TB treatment, highlighting the difficult management of this cohort. Our patients received moxifloxacin for a mean of 6 months. AEs were correlated to moxifloxacin on the basis of the

type of AE reported and on the temporal correlation with administration, withdrawn, re-challenge. Overall, this quinolone was well tolerated, even if at least one out of four patients reported an AE. Almost 20% (7 patients) reported gastrointestinal disorders (mainly nausea and vomiting) due to moxifloxacin. This proportion of AEs seems to be higher compared to the frequency of nausea and vomiting in patients affected by respiratory tract infections treated with quinolones for 5–14 days,[8] but it may be explained by the longer duration of the treatment and the combination with other drugs. Two of these patients required the discontinuation of the drug, whilst in 5 patients the AEs were transitory, resolved by the discontinuation of moxifloxacin and without preventing the re-introduction of the drug in the anti-TB treatment.

Quinolones are known to penetrate the hematoencephalic barrier, and this can explain some AE occurring in our cohort of patients, like dizziness, tremors and insomnia, as well as asthenia and anorexia. Three out of 4 of our patients who needed a discontinuation of the drug complained these AEs. Considering the chondrotoxicity of quinolones,[23] it is not surprising that 2 patients of our cohort reported arthalgia. The case of vaginitis can be explained by the prolonged effect of moxifloxacin on the normal vaginal flora.[24] One patient reported eye irritation: corneal deposits of quinolones were also described,[25] and this should be taken in consideration when prescribing long-term quinolones.

A recent study[26] discussed the important issue of the new quinolones safety in patients at increased risk of cardiac toxicity. None of our patients reported serious cardiac AEs: EKG data were available only for 8 patients and none repeated the EKG during the study period. Moxifloxacin showed safe in our limited experience. However, the patients described in our study were mostly young and had no risk for cardiac complications.

The analysis of outcomes revealed a lower success rate for patients treated with moxifloxacin modified regimens because of MDR TB, compared to patients treated for intolerance to first line drugs or resistance other than MDR TB, highlighting the tolerability of the drug until the end of the treatment in patients who already experienced severe AE.

Although larger studies are necessary to define more clearly the role of moxifloxacin in the treatment of MDR and complicated TB cases, the results of our study suggest that the long-term use of the drug is safe, most of the AEs reported being mild and reversible (discontinuation of the drug necessary only in 4 patients, complaining mostly gastrointestinal and Central Nervous System AEs).

References

1. Espinal MA. The global situation of MDR-TB. *Tuberculosis (Edinburgh)* 2003;**83**(1–3):44–51.
2. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *J Am Med Assoc* 2000;**283**(19):2537–45.
3. Migliori GB, Espinal M, Danilova ID, Punga VV, Grzemska M, Raviglione MC. Frequency of recurrence among MDR-tB cases 'successfully' treated with standardised short-course chemotherapy. *Int J Tuberc Lung Dis* 2002;**6**(10): 858–64.
4. O'Brien RJ. Studies of the early bactericidal activity of new drugs for tuberculosis: a help or a hindrance to antituberculosis drug development? *Am J Respir Crit Care Med* 2002;**166**(1):3–4.
5. Treatment of tuberculosis. *MMWR Recomm Rep* 2003;**52** (RR-11):1–77.
6. Mukherjee JS, Rich ML, Socci AR, Joseph JK, Viru FA, Shin SS, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. *Lancet* 2004;**363**(9407):474–81.
7. Garcia-Tapia A, Rodriguez JC, Ruiz M, Royo G. Action of fluoroquinolones and Linezolid on logarithmic- and stationary-phase culture of Mycobacterium tuberculosis. *Chemotherapy* 2004;**50**(5):211–3.
8. Ball P, Stahlmann R, Kubin R, Choudhri S, Owens R. Safety profile of oral and intravenous moxifloxacin: cumulative data from clinical trials and postmarketing studies. *Clin Ther* 2004;**26**(7):940–50.
9. Tahaoglu K, Torun T, Sevim T, Atac G, Kir A, Karasulu L, et al. The treatment of multidrug-resistant tuberculosis in Turkey. *N Engl J Med* 2001;**345**(3):170–4.
10. Lubasch A, Erbes R, Mauch H, Lode H. Sparfloxacin in the treatment of drug resistant tuberculosis or intolerance of first line therapy. *Eur Respir J* 2001;**17**(4):641–6.
11. Dawe RS, Ibbotson SH, Sanderson JB, Thomson EM, Ferguson J. A randomized controlled trial (volunteer study) of sitafloxacin, enoxacin, levofloxacin and sparfloxacin phototoxicity. *Br J Dermatol* 2003;**149**(6):1232–41.
12. Richeldi L, Covi M, Ferrara G, Franco F, Vailati P, Meschiari E, et al. Clinical use of Levofloxacin in the long-term treatment of drug resistant tuberculosis. *Monaldi Arch Chest Dis* 2002;**57**(1):39–43.
13. Yew WW, Chan CK, Leung CC, Chau CH, Tam CM, Wong PC, et al. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. *Chest* 2003;**124**(4):1476–81.
14. Rodriguez JC, Ruiz M, Lopez M, Royo G. In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against Mycobacterium tuberculosis. *Int J Antimicrob Agents* 2002; **20**(6):464–7.
15. Gosling RD, Uiso LO, Sam NE, Bongard E, Kanduma EG, Nyindo M, et al. The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med* 2003;**168**(11):1342–5.
16. Valerio G, Bracciale P, Manisco V, Quitadamo M, Legari G, Bellanova S. Long-term tolerance and effectiveness of moxifloxacin therapy for tuberculosis: preliminary results. *J Chemother* 2003;**15**(1):66–70.

17. Migliori GB, Centis R, Fattorini L, Besozzi G, Saltini C, Orefici G, et al. Monitoring the quality of laboratories and the prevalence of resistance to antituberculosis drugs: Italy, 1998–2000. *Eur Respir J* 2003;**21**(1):129–34.
18. Maher D, Chaulet P, Spinaci S, Harries A. Treatment of tuberculosis: guidelines for national programmes, 3rd ed. Geneva, Switzerland, 2003.
19. Veen J, Perrocheau A, Schwoebel V. Surveillance of tuberculosis in the WHO European region in 1995: results of the feasibility study. *Euro Surveill* 1998;**3**(1):2–5.
20. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh Jr CR. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993;**328**(8):527–32.
21. Pletz MW, De Roux A, Roth A, Neumann KH, Mauch H, Lode H. Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. *Antimicrob Agents Chemother* 2004;**48**(3):780–2.
22. Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an in vitro pharmacodynamic infection model and mathematical modeling. *J Infect Dis* 2004;**190**(9):1642–51.
23. Burkhardt O, Kohnlein T, Pap T, Welte T. Recurrent tendinitis after treatment with two different fluoroquinolones. *Scand J Infect Dis* 2004;**36**(4):315–6.
24. Weis M, Hendrick K, Tillotson G, Gravelle K. Multicenter comparative trial of ciprofloxacin versus cefuroxime axetil in the treatment of acute rhinosinusitis in a primary care setting. Rhinosinusitis Investigation Group. *Clin Ther* 1998; **20**(5):921–32.
25. Castillo A, Benitez del Castillo JM, Toledano N, Diaz-Valle D, Sayagues O, Garcia-Sanchez J. Deposits of topical norfloxacin in the treatment of bacterial keratitis. *Cornea* 1997; **16**(4):420–3.
26. Morganroth J, Dimarco JP, Anzueto A, Niederman MS, Choudhri S. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with community-acquired pneumonia. *Chest* 2005;**128**:3398–406.